Serum Interleukin 27 Level in Pediatric Patients with Idiopathic Thrombocytopenic Purpura (ITP)

Thesis

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بسم الله الرحمن الرحيم

وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ
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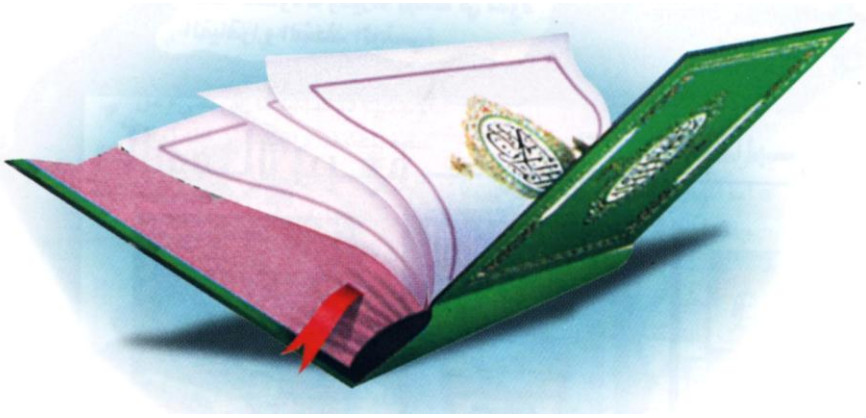

صدق الله العظيم

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List of Abbreviations

Abb.	Full term
AML	*Acute myeloid leukemia*
Anti-D	*Anti-D immunoglobulin*
APC	*Antigen presenting cells*
ASH	*American Society of Hematology*
AUC	*Area under curve*
CITP	*Chronic ITP*
CLF	*Cytokine-like factor 1*
COPD	*Chronic obstructive pulmonary disease*
CR	*Complete remission*
EAE	*Experimental autoimmune encephalomyelitis*
EAU	*Experimental autoimmune uveitis*
Ebi3	*Epstein–Barr virus-induced gene 3*
EBI3	*Epstein–Barr-induced protein 3*
FcγRI	*Fc receptors: high affinity*
Foxp3	*Factor forkhead-box p3*
IBD	*Inflammatory bowel disease*
IBLS	*ITP Bleeding Scale*
ICAM-1	*Intercellular Adhesion Molecule-1*
ICH	*Intracranial hemorrhage*
ICIS	*Intercontinental Childhood ITP Study Group*
IFNG	*Interferon gamma*
IL	*Interleukin*
IL-27	*Interleukin-27*
IQR	*Inter-quartile range*
ITP	*Immune thrombocytopenic purpura*
ITP	*Primary immune thrombocytopenia*

List of Abbreviations cont...

Abb.	Full term
IVIG	*Intravenous immunoglobulin*
LFA-1	*Lymphocyte function-associated antigen 1*
MAPK	*Mitogen-activated protein kinase*
mRNA	*Messenger Ribonucleic acid*
MS	*Multiple sclerosis*
NPV	*Negative predictive value*
PBMCs	*Peripheral blood mononuclear cells*
PCR	*Polymerase chain reaction*
PD-L1	*Programmed death-ligand 1*
PPV	*Positive predictive value*
RFLP	*Restriction fragment length polymorphism*
ROC	*Receiver operating characteristic curve*
RORC	*RAR-related orphan receptor C*
SNPs	*Single-nucleotide polymorphism*
SPSS	*Statistical Package for Social Science*
STAT	*Signal transducer and activator of transcription*
TC1 cells	*Type 1 CD8(+) T cells*
TFH	*Follicular B Helper T cells*
Th	*T-helper*
TLR2	*Toll-like receptor 2*
TLR4	*Toll-like receptor 4*
VNN-1	*Vanin-1*
WHO	*World Health Organization*

Abstract

Background: Immune thrombocytopenia (ITP) is a common autoimmune disorder characterized by immune-mediated accelerated platelet destruction and resulting in isolated thrombocytopenia.

Aim of the Work: This study aims at evaluation of prognostic value of interleukin 27 (IL-27) serum level in pediatric patients with acute, persistent and chronic ITP and its relationship with treatment response.

Patients and Methods: The study was conducted on 43 patients with ITP from Pediatric Hematology Clinic, Pediatric Hospital, Ain Shams University and 20 age and sex matched normal children as the control group. All the studied children were subjected to through history, clinical examination and laboratory investigations, including complete blood count (CBC) and IL-27 serum level using ELISA technique.

Results: The study revealed a significant decrease IL-27 level in ITP patients compared to control group with no significant difference between different categories of ITP as regards IL-27 serum levels. There was no significant relation between category of disease and platelet count, hemoglobin level and IL-27 during blood sampling ($p=0.261$, 0.426, 0.558 respectively). More than 50% of studies ITP patients received steroids; 76.7% of them did not respond to steroid therapy. There was a positive correlation between IL-27 level and duration of steroid intake in ITP patients ($r=0.406$, $p=0.04$).

Conclusion: The decrease in serum IL27 level in different categories of pediatric ITP patients might suggest its involvement in the pathophysiological process of ITP. IL-27 level might play a role in patients response to corticosteroid therapy.

Keywords: Serum Interleukin 27, Idiopathic Thrombocytopenic Purpura

INTRODUCTION

Primary immune thrombocytopenia (ITP) is a common autoimmune disorder characterized by immune-mediated accelerated platelet destruction and suppressed platelet production and resulting in isolated thrombocytopenia ***(Johnsen et al., 2012).***

Acute ITP usually follows viral upper respiratory tract infection and resolves within 3 months or less ***(Hamiel et al., 2016).***

Persistant ITP is a type of ITP, that lasts from 3 to 12 months, while chronic ITP lasts for more than 12 months ***(Mccrae et al., 2013).***

Concepts surrounding the mechanisms of thrombocytopenia in ITP have shifted from the traditional view of increased platelet destruction mediated by autoantibodies to more complex mechanisms in which impaired platelet production, T-cell-mediated effects, and disturbed cytokine profiles play a role ***(Provan et al., 2010).***

Interleukin-27 (IL-27), a heterodimeric cytokine composed of *Epstein–Barr virus-induced gene 3 (Ebi3)* and *IL-27p28*, belongs to the IL-6/IL-12 family cytokines. Its receptor is composed of *gp130* and IL-27 receptor α chain (*IL-27Rα*, also known as *WSX1* or *TCCR*) that activates the *Janus kinase (JAK)/signal transducer and activator of transcription (STAT)*

pathway and the *mitogen-activated protein kinase (MAPK)* pathway ***(Iwasaki et al., 2015).***

IL-27 is a cytokine with both proinflammatory and anti-inflammatory effects. There is an evidence suggesting various roles of IL-27 in autoimmune diseases in humans (e.g. rheumatoid arthritis, Crohn's disease, psoriasis, and multiple sclerosis) ***(Bosmann and Ward, 2013).***

Many studies focused on the role of IL-27 in ITP, however, the role of IL-27 in ITP and its impact on disease response have not been fully elucidated and are still controversial ***(Li et al., 2015).***

AIM OF THE WORK

This study aims at measurement of the level of interleukin 27 in pediatric ITP patients, to compare between its different levels in acute and chronic ITP and to evaluate its relation to treatment response, and to check any prognostic value of serum IL 27 level.

Chapter (1)

IDIOPATHIC THROMBOCYTOPENIC PURPURA

Definition

Idiopathic thrombocytopenic purpura (ITP), also known as primary immune thrombocytopenic purpura, immune thrombocytopenia and autoimmune thrombocytopenic purpura, is defined as an acquired hemorrhagic condition characterized by the accelerated clearance of platelets caused by antiplatelet autoantibodies such as anti-glycoprotein ***(Nomura, 2016)***.

It is isolated thrombocytopenia with normal bone marrow and in the absence of other causes of thrombocytopenia. ITP has two distinct clinical syndromes, manifesting as an acute condition in pediatrics ***(Lyu et al., 2015).***

ITP mainly affects the platelet count in the blood. ITP can be classified as acute, chronic or recurrent. The acute form is a temporary condition, which persists for less than 3 months and affects mainly children while the chronic stage might last more than 12 months and affects adults more, the recurrent form is multiple incidents of thrombocytopenia in the period of over 3 months. ITP results from an auto-immune mechanism or from impaired thrombopoiesis ***(Ozkan et al., 2015).***

Etiology

In most cases, the cause of ITP is unknown. It is not contagious, meaning a child cannot "catch it" from playing with another child with ITP. It is also important to know that nothing the parents, nor the child, did caused the disorder ***(Chen et al., 2010).***

Often, the child may have had a virus or viral infection about three weeks before developing ITP. It is believed that the body, when making antibodies against a virus, "accidentally" also made an antibody that can stick to the platelet cells. The body recognizes any cells with antibodies as foreign cells and destroys them. That is why ITP is also referred to as immune thrombocytopenic purpura ***(Godeau et al., 2013).***

The environmental factors can modify the susceptibility to this disease, in part, through modulating and inducing some epigenetic changes. Epigenetics has become an exciting and evolving field of research, and the roles in autoimmune disease were extensively discussed ***(Chen et al., 2010).***

Platelets are essential for the formation of a blood clot. Blood clots consist of a mass of fibers and blood cells. Platelets travel to a damaged area and stick together to form a plug, whenever a person is cut, for example. If there are not enough platelets, a clot cannot be formed, resulting in more bleeding ***(Shan et al., 2014).***